Regulation of Intravenous Nicotine Self-Administration

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We have obtained reliable nicotine self-administration in rats using a limited-access FR5 schedule. Self-administration behavior in these studies is dose-dependent and produces nicotine intake as high as 0.5 mg/kg/hour. However, the dose-dependency of nicotine self-administration is different from that of other drugs. With nicotine, compensatory increases in responding typically do not occur as the unit dose of the drug is decreased. There is, however, a decrease in responding at high doses. Therefore, analogous to cigarette smoking by humans, regulation of nicotine intake in this IV self-administration paradigm is most apparent at the upper end of the intake curve.

This paradigm has been used to investigate some of the neurochemical substrates in the regulation of nicotine reinforcement, particularly opiate and dopaminergic systems. Based upon data from experiments in which animals were pre-treated with the antagonist naltrexone before self-administration sessions, we have concluded that an endogenous opiate system is not involved in nicotine reinforcement. However, as detailed below, evidence suggests that there is a dopaminergic substrate in nicotine self-administration.

In one study, dopamine antagonists were administered acutely prior to self-administration sessions. The effects of these antagonists on nicotine self-administration were compared to their effects on operant responding maintained by cocaine and by food, and locomotor activity after saline and nicotine injections. Pre-treatment with the D2 antagonist spiperone decreased nicotine self-administration dose-dependently. Spiperone did not alter the ability of the animals to perform, since nicotine-maintained responding was not reduced during the first half of the one-hour sessions, but decreased in the latter half. Locomotor activity after nicotine, but not after saline, was also reduced by spiperone treatment, whereas cocaine self-administration was increased.

Decreases in nicotine self-administration were produced by the D1 antagonist SCH23390 as well. However, SCH23390 also reduced operant responding maintained by food, and both the food and nicotine response patterns showed that general rate-decreasing effects could not be ruled out as the cause. The D1 antagonist also produced decreases in locomotor activity after either saline or nicotine, further evidence that the compound may have behavior-decreasing properties. Nonetheless, treatment with low doses of SCH23390 produced small compensatory increases in cocaine-maintained behavior.

Overall, therefore, these data demonstrate that pharmacological manipulation of dopamine receptors, particularly those of the D2 subtype, can alter nicotine self-administration and locomotor activity. However, the effects on self-administration are not analogous to the effect of dopamine antagonists on self-administration of cocaine. The difference may be due to differences in the regulation of self-administration of the two drugs, or may indicate that the effect on nicotine self-administration is not due to a reduction in reinforcement per se.

In another experiment, we examined whether the mesolimbic dopamine projection is involved in nicotine self-administration. After bilateral lesions of the nucleus accumbens with 6-hydroxydopamine, nicotine self-administration was reduced by approximately 75% compared to sham-operated animals. Post-mortem analysis of brain tissue showed that the lesion had produced a 93% depletion of dopamine in the accumbens and a 25% depletion in the caudate-putamen. The dopaminergic projection to the nucleus accumbens may therefore play an important role in regulating nicotine self-administration.